

5 What is claimed is:

1. A mutant mammalian G-protein coupled receptor having a sequence which varies from a wild type G protein-coupled receptor having a wild type amino acid sequence comprising an amino acid motif [X₁X₂X₃X₄] lying near the carboxy terminal end of said domain, wherein:

X₁ denotes an amino acid residue at position 1 of said motif and is selected from the group consisting of Phe, Leu, Val, and Tyr;

X₂ denotes an amino acid residue at position 2 of said motif and is selected from the group consisting of Phe, Lys and Gln;

X₃ denotes an amino acid residue at position 3 of said motif and is selected from the group consisting of Leu, Arg, Glu, Asn, Gln, Ser, Ala, Leu ; and

X₄ denotes an amino acid residue at position 4 of said motif and is selected from the group consisting of Ala, Cys, Asp, Glu, Gly, Ser, Thr and Tyr; and

wherein said mutant receptor comprises a seventh transmembrane domain with a carboxy terminal end;

at least one point mutation at a position in said amino acid motif; such that upon interaction with a ligand to modulate a signal transduction pathway in a cell, a signal generated by said mutant receptor is greater than a signal generated upon interaction of said ligand with a wild type G protein-coupled receptor.

2. The receptor of claim 1, wherein said cell is a yeast cell.

3. The receptor of claim 2, wherein said receptor acts as a surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of said cell.

4. The receptor of claim 2, wherein said cell belongs to the species *Saccharomyces cerevisiae*.

5. The receptor of claim 1, wherein said cell is a mammalian cell.

6. The receptor of claim 1, wherein said receptor containing said amino acid motif with no point mutation thereon generates no detectable signal.

7. The receptor of claim 1, wherein said point mutation comprises mutagenization at position 4 of said amino acid motif to Arg or to Lys.

Sub. 5
A3
~~8. The receptor of claim 1, comprising an IL8A receptor.~~

9. The receptor of claim 8, wherein said point mutation is selected from the group consisting of : Arg to Trp at position 73, Met to Ile at position 246; and Gly to Arg at position 320.

10. The receptor of claim 8, wherein said ligand is interleukin 8 (IL8) or melanoma growth-stimulating activity-alpha (MGSA/GRO α).

Sub. 15
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11. The receptor of claim 1 comprising a human receptor.

12. The receptor of claim 11 selected from the group consisting of human galanin-1 receptor, somatostatin receptor type I, somatostatin receptor type II, somatostatin receptor type III, and human nociceptin receptor.

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13. The receptor of claim 12, which is human galanin-1 receptor.

14. The receptor of claim 13, comprising an amino acid sequence LAYSNSSVNPIIYAFLSEN[FRKR]YKQV wherein said mutant amino acid motif within said sequence is [FRKR].

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15. A recombinant yeast cell having a mutant form of a mammalian G protein-coupled receptor expressed in a membrane of said yeast cell, said mutant receptor having a sequence that varies from a wild type G protein-coupled receptor having a wild type amino acid sequence comprising an amino acid motif [X₁X₂X₃X₄] lying near the carboxy terminal end of said domain, wherein:

X₁ denotes an amino acid residue at position 1 of said motif and is selected from the group consisting of Phe, Leu, Val, and Tyr;

35 X₂ denotes an amino acid residue at position 2 of said motif and is selected from the group consisting of Phe, Lys and Gln;

X₃ denotes an amino acid residue at position 3 of said motif and is selected from the group consisting of Leu, Arg, Glu, Asn, Gln, Ser, Ala, Leu ; and

X₄ denotes an amino acid residue at position 4 of said motif and is selected from the group consisting of Ala, Cys, Asp, Glu, Gly, Ser, Thr and Tyr; and
40 wherein said mutant receptor comprises:

a seventh transmembrane domain with a carboxy terminal end;

and

5 at least one point mutation at a position on said amino acid motif;
wherein said mutant receptor acts as a surrogate for an endogenous yeast pheromone
receptor in a pheromone response pathway of the yeast cell, such that upon interaction
with a ligand to modulate signal transduction in said pheromone response pathway, a
signal generated by said mutant receptor is greater than a signal generated upon
10 interaction of said ligand with a wild type G protein-coupled receptor.

16. The yeast cell of claim 15, comprising a human receptor.

17. The yeast cell of claim 16, wherein said receptor is selected from the
15 group consisting of human galanin-1 receptor, somatastatin receptor type I, somatastatin
receptor type II, somatastatin receptor type III, and human nociceptin receptor.

18. The yeast cell of claim 15, comprising an IL8A receptor.

19. The yeast cell of claim 16, which expresses a mammalian, chimeric,
20 and/or mutant G protein subunit.

20. The yeast cell of claim 19, which expresses a mammalian, chimeric,
and/or mutant G α subunit.

21. The yeast cell of claim 20, which expresses a GPA41-G α_{i3} subunit.

22. The yeast cell of claim 20, which expresses a GPA41-G α_{i1} or GPA41-
G α_{i2} subunit.

23. The yeast cell of claim 19, which expresses a STE18-G γ_2 subunit.

24. The yeast cell of claim 16, which expresses a mammalian G α_s E10K
subunit.

25. The yeast cell of claim 16, which expresses a mammalian G α_s D229S
subunit or a mammalian G α_s E10K + D229S subunit.

26. The yeast cell of claim 15, which is a mutant cell having a pheromone
40 response pathway that is desensitized at slower rate than a wild type strain under the
same conditions of continuous stimulation of the pheromone response pathway.

- 5 27. The yeast cell of claim 15, which has a *ste14* mutation.
28. The yeast cell of claim 15, which has a *ste2* or *ste3* mutation.
29. The yeast cell of claim 15, wherein an endogenous pheromone gene is not
10 functionally expressed in the yeast cell.
30. The yeast cell of claim 15, wherein an endogenous *FAR1* gene is not
functionally expressed in the yeast cell.
- 15 31. The yeast cell of claim 15, wherein an endogenous *SST2* gene is not
functionally expressed in the yeast cell.
32. The yeast cell of claim 15, which further comprises a detectable or
selectable marker that is activated by a pheromone response pathway of the yeast cell.
20 33. The yeast cell of claim 32, wherein the selectable marker comprises a
pheromone-responsive promoter operably linked to a selectable gene.
34. The yeast cell of claim 33, wherein the pheromone-responsive promoter
25 is the *FUS1* promoter.
35. The yeast cell of claim 33, wherein the marker gene is a HIS 3 gene or a
LacZ gene.
- 30 36. The yeast cell of claim 15, which further comprises a heterologous
polypeptide, wherein the heterologous polypeptide is transported to a location allowing
interaction with the region of said receptor expressed in the cell membrane and wherein
modulation of the signal transduction of said receptor by the heterologous polypeptide
provides a detectable signal.
- 35 37. The yeast cell of claim 36, wherein the heterologous polypeptide includes
a signal sequence.
38. The yeast cell of claim 37, wherein the signal sequence corresponds to a
40 leader peptide of the *Saccharomyces cerevisiae* α factor or α -factor.

5 39. The yeast cells of claim 15, which belong to the species *Saccharomyces cerevisiae*.

 40. A method for identifying a modulator of a mammalian G-coupled protein receptor expressed by a yeast cell, comprising:

- 10 (i) contacting a mixture of yeast cells as claimed in claim 15 with a test compound;
- (ii) allowing cells within the mixture to generate a detectable signal; and
- (iii) identifying the test compound as a modulator of said receptor expressed by the yeast cell.

15 41. A method for identifying a modulator of a mammalian G-coupled protein receptor expressed by a yeast cell, comprising:

- (i) contacting a mixture of yeast cells as claimed in claim 2 with a test compound for a period of time sufficient for generation of a detectable signal; and
- 20 (ii) determining if said test compound is a modulator of said receptor by detecting the presence or absence of a signal.

 42. A method of identifying a modulator of a mammalian G-coupled protein receptor expressed by a mammalian cell, comprising:

- 25 (i) contacting a mixture of mammalian cells as claimed in claim 5 with a test compound for a period of time sufficient for generation of a detectable signal; and
- (ii) determining if said test compound is a modulator of said receptor by detecting the presence or absence of a signal.

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